been added as an elected species. Claim 4 has been canceled. It is believed that claims 1-3, 5 and 7-23 read on the species of claim 24 and only claim 6 should be withdrawn as being directed to a non-elected species. Thus, claims 1-3, 5 and 7-24 remain under consideration in the present application and no claim presently stands allowed.

With respect to the gene sequence included with this amendment, the content of the printed paper and of the computer readable copy enclosed are the same and they contain no new matter. The name of the assignee corporation referred to has been changed to Biovation Limited and a copy of a certificate showing that name change is also enclosed for the Examiner's information and records.

The material presented in the Office Action in relation to the election requirement is not clear. For example, no claims have been enumerated as being withdrawn from further consideration by the Examiner under 37 CFR § 1.142(b) (page 3). In addition, the previous telephone election did not allow a complete analysis of the specification and therefore, referring to item 8, for example, in retrospect a somewhat different election would be made. In any event, it is the opinion of the applicant that the chimaeric peptides claimed generically are sufficiently related that the claims should be examined as a unitary invention. Whereas the polypeptide of claim 2 comprises a translocation portion and an optional signal portion, this is also covered generically in claim 1.

It is believed that the amended claims overcome each of the rejections under 35 USC § 112 raised by the Examiner. With respect to item A, the term "portion thereof" in claims 1 and 3 (not claim 2) is not limited to Fab and F(ab)2 fragments of an immunoglobulin molecule. As set out on page 3 of the specification, it includes portions of immunoglobulin molecules which retain some degree of specific binding affinity, including F_{ab}, F_v (separate V_H and V_L which combine), SCA and scFv (single chain F_vs in which V_H and V_L are connected by a linker) fragments. It may also include other configurations of F_vs such as multivalent F_vs or parts of an F_v, such as the V_H domain alone or peptides from specific CDRs (complementarity determining regions) such as CDRH3. These alternatives are well known to those skilled in the art. The words "an effective" have been deleted in the enclosed claims; the phrase "having specific binding affinity for a eukaryotic target cell surface component" is believed to render the term "portion thereof" sufficiently clear.

With respect to item C, the term "modulate" as used, is to be given its normal meaning of "regulate" or "adjust" and this, of course, includes increasing and decreasing. Thus, the term includes, for example, initiating a T cell response, blocking a T cell response, enhancing a T cell response or diminishing a T cell response.

With respect to item D, in claim 9, the term "capable of exerting an immunomodulatory effect" includes the capability of

increasing or decreasing the immune response. See, for example, the descriptive material on page 5 of the specification.

With respect to item E, the term "biological effect" has been replaced by "immunodulatory effect". This term is believed clear and, in claim 2, for example, is not limited to eliciting an immune response to the specific peptide. The term is believed to convey the necessary technical information to enable one skilled in the art to put the invention into practice. The claim specifies that the chimaeric polypeptide comprises a peptide which exerts an immunomodulatory effect, and requires that the result of internalisation of the effector and translocation portions is to allow the peptide to exert its immunomodulatory effect.

It would be clear to one skilled in the are that, for example, presentation of peptides by MHC molecules can exert a range of effects dependent on the cell type, peptide type and MHC type. The term "immunomodulatory effect" is a term that would reasonably be understood in this art to encompass such effects, including, for example, T cell activation or tolerance. Page 5, lines 1-5, indicates that the peptides that are delivered into cells either may bind to MHC molecules or may bind "to specific intracellular molecules to produce effects such as blocking intracellular protein-protein interactions (such as those involved in intracellular signaling)".

Immunomodulatory effects are referred to in several places in the description, for example, page 1, line 10 "induction or

inhibition of an immune response", page 3 (quoted above), page 4, lines 14 and 15 "immunomodulatory effect", page 4, line 18 "to activate CTLs to subsequently destroy the cancer cells", page 4, line 21 "to induce tolerance", page 4, line 22, antagonise the disease-associated T cell activation.", page 4, line 31 "immune response". Pages 5 to 6 refer to a number of types of immunomodulatory response induced by molecules of the invention.

With respect to item F, it is believed that it is not necessary to define the maximum and minimum lengths of the peptide in claim 1. As is well known in the art, the core peptide sequence that binds within MHC class I or class II binding grooves is usually 9-10 amino acids long, but for at least class II, longer peptides may attach to the groove. Although the peptide may be trimmed, the final range of peptide lengths may be longer for class II than one, but in neither case is it restricted to 9-10 amino acids. For example, because the peptides bind in the groove via certain recognized anchor residues, smaller peptides can bind selectively, possibly as small as 5 amino acids.

With regard to item 7, the multiple dependency of the claims has been amended to be in conformance with US practice. With respect to the English language, however, we can find no provision requiring the requested change and believe British English to be fully proper. In this regard, it is believed that anyone sufficient familiar with the language should accept these

minor variences particularly with present attempts to harmonize patent practice around the world in view of WTO/GATT/TRIPS, etc.

With respect to the rejection of the claims on the merits under 35 USC § 103(a), it is noted that the Examiner has presented a rejection based upon a combination of some seven references. This rejection is respectfully traversed. Reasons to support this position are enumerated next below.

Although the molecule of Donnelly et al (EP 0 532 090 A2) includes a cellular recognition portion, this is not selective for particular cell types, in contrast to the chimaeric molecules of the present invention. Moreover, the cellular recognition portion and translocating portion are derived from the same natural molecule and are therefore not from different sources, as required by claim 2.

Similarly, for example, the molecules described by Fawell et al (1994) PNAS 91, 664-668 are not selective for a specific cell type. The molecules are taken up by several distinct cell types; not, for example, on page 664, column 2, it is stated that "[d]elivery is independent of cell type". Thus, neither Donnelly et al nor Fawell et al teach chimaeric proteins that may be targeted to specific cells via specific binding affinity for a target cell component. Further, there is no description in Fawell of any effector portion capable of exerting an immunomodulatory effect. These references do not contain any motivation for the skilled person to combine them and even if

combined, these references do not teach chimaeric polypeptides with the features specified in claims 1 or 2.

It does appear that Fawell et al mentions in the final sentence the possibility of using tat to introduce peptide epitopes into cells to stimulate class I major histocompatibility complex responses, but no examples of this are described or suggested.

Murphy (US 5,668,255) and Zimmerman et al (US 5,652,341) appear to teach molecules which bind to specific cells, as stated by the Examiner. However, amended claim 2 is clearly novel over Murphy, as Murphy does not give any indication that the effector portion may comprise a peptide which exerts an immunomodulatory effect.

Zimmerman et al attaches an antigenic peptide to the T cell specific binding ligand. There is no indication that the molecule is internalised, a feature required by claims 1 and 2. There is no indication that targeting molecules to an APC (antigen presenting cell) is beneficial; the passage cited by the Examiner in column 4, lines 46-55, for example, merely indicates that a T cell specific ligand that is also located on or binds to APCs is not excluded. This document would not provide any motivation to the skilled person to select an APC as a target cell type.

The Examiner states that Lowenadler et al (1992) Mol Immunol 29, 1195 teaches a chimaeric protein comprising a cellular binding portion; the Ig-G binding domain of protein A. With all

due respect, the Examiner is believed to be incorrect on this point. The protein A domain is not a cellular binding portion. It is used for purification of the molecule on IgG-sepharose (page 1186, second column, first paragraph). Protein A will bind free IgG but not cell bound IgG or IgM. Thus, this document does not teach a molecule which has specific binding affinity for a specific target cell component.

The molecules of Roemer et al (1993) PNAS 20, 9252-9246 are targeted to the oestrogen receptor hormone, which is an intracellular molecule; there is also no indication that an immunological effect was sought or achieved. Thus, this paper appears distant from the field of the present invention. The Examiner's comments on the content of Noguchi et al (1994) PNAS91, 3171-3175 appear to be correct, however, there is nothing in this paper that would lead the skilled person to combine its teaching with any of the other cited references.

The Examiner has cited a large number of documents, but it does not appear that there is any motivation to combine the teachings of these documents. Moreover, even if the documents were combined, it is not seen how the skilled person would arrive at the present invention. The Examiner has been obliged to "mosaic" a large number of references in order to attempt to demonstrate a chain of non-inventive steps purporting to lead to the invention. The Examiner has not demonstrated that the proposed chain leads to the present invention, and the need for a large number of references and developmental steps serves in

itself as an indication of the inventive nature of the claimed molecules and methods.

Please note also as an overview that the invention resides at least partly in the provision of molecules that lead to effective immunomodulation as a consequence of being targeted to specific cells, for example APCs. These molecules may therefore be effective modulators of immune responses, for example effective vaccines. Effective immunomodulation may be further facilitated by the provision of an effector portion consisting of one or more copies of an immunogenic peptide and/or by inclusion of a signal portion that directs the effector portion to a particular cellular compartment, such as the cytoplasm, so that it can exert its immunomodulatory effect, for example, via presentation of peptides on MHC molecules, particularly MHC class I molecules.

Proteins introduced externally to cells, for example APCs, are not efficiently taken up, processed and presented by MHC molecules for stimulation of T cells. Uptake of the proteins is inefficient unless these proteins are provided in certain particles or aggregates; even then, the APC (for example) has to find the protein rather than the protein find the cell as in the present invention. Further, the molecules of the present invention achieve efficient processing and presentation by MHC class I of peptides from the effector portion for subsequent activation of CTLs, for example by the use of a signal peptide

that allows the effector portion to enter the cytoplasm where it can be processed.

It is therefore submitted that not only is the elected species patentable, but that all the claims, including all generic claims, are believed novel and inventive over the above-cited documents. Reconsideration and early allowance of the claims is respectfully requested.

Respectfully submitted,

NIKOLAI, MERSEREAU & DIETZ., P.A.

C. G. Mersereau
Registration No. 26,205
Attorneys for Applicant(s)
820 International Centre
900 Second Avenue South
Minneapolis, MN 55402
(612) 339-7461

CERTIFICATE OF MAILING

I hereby certify that the foregoing Amendment in response to the Official Action of August 4, 1998, together with a Petition for a two-month Extension of Time and a check in the amount of $190.00, in application Serial No. 08/737,457, filed on November 13, 1996, of Donald L.N. Cardy et al, entitled "IMPROVEMENTS IN OR RELATING TO PEPTIDE DELIVERY" is being deposited with the U.S. Postal Service as First Class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, postage prepaid, on January 4, 1999.

Barbara L. Davis
Secretary to C. G. Mersereau
Attorney for Applicant

Date of Signature: January 4, 1999